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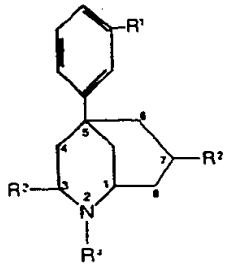
(54) Phenylmorphans, processes for their preparation, pharmaceutical compositions containing them, and 4-phenyl-tetrahydro-pyridines.

(57) A novel 5-phenylmorphan compound having the formula



VI

wherein:

R^1 is hydrogen, hydroxy or C_1–C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1–C_5 alkyl or CH_2C_2–C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1–C_{10} alkyl, phenyl C_1–C_3 alkyl, CH_2C_2–C_9 alkenyl, or CH_2C_3–C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof are disclosed. These compounds are useful in the treatment of pain.

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TITLE MODIFIED -1-
see front page

PHENYLMORPHANS, INTERMEDIATES AND METHOD OF PREPARATION

Novel 5-phenylmorphans are useful for their analgesic activity. A process for their preparation from 1,2,5,6-tetrahydro-4-phenyl-pyridines is disclosed.

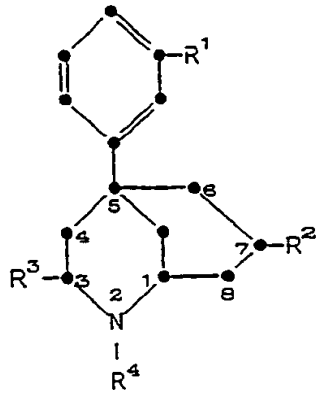
Analgesics are widely used in the treatment of mild pain due to CNS disorders and of more severe pain due to diseases such as cancer. Many of the agents commonly used to relieve instances of severe pain are extremely dangerous due to their potency and to their addicting properties. Morphine is among such analgesic agents, and causes severe physical dependence. Even with such drawback, morphine is extensively used simply because of the non-existence of a more desirable agent. A great deal of research has been devoted, however, to finding compounds capable of alleviating severe pain to the degree accomplished with morphine, but which display little or no physical dependence capacity. Among the more recent discoveries is the series of compounds referred to generally as the "phenylmorphans". May and Murphy reported that racemic 5-(3-hydroxyphenyl)-2-methylmorphan possesses an analgesic potency nearly equivalent to that of morphine, J. Org. Chem., 20, 1197 (1955). May and Takeda later reported that the (-)isomer of 5-(3-hydroxyphenyl)-2-methylmorphan is an analgesic with morphine-like potency but with no physical dependence capacity, J. Med. Chem., 13, 805 (1970).

One of the major difficulties with the early syntheses of this extremely potent series of compounds

was the low overall yields and the difficulty in handling the intermediates. Rogers and May recently reported an improved synthesis of (-)-5-(3-hydroxyphenyl)-2-methylmorphan, but still the overall yield was only one percent, J. Med. Chem., 17, 1328 (1974). A number of novel 5-(3-hydroxyphenyl)-2-(substituted)-morphans have been prepared and evaluated by Ong and co-workers, J. Med. Chem., 17, 133 (1974). None, however, were as potent as the 5-(3-hydroxyphenyl)-2-methylmorphan.

To date, no phenylmorphans having various substituents at positions other than the morphan 2-position have been prepared. The purpose of this invention is to provide certain 5-phenylmorphans having alkyl and alkenyl substituents at the 3 and 7-positions. Another purpose of the invention is to provide an improved synthesis of both new and known phenylmorphans.

This invention provides a 5-phenylmorphan compound having the formula



VI

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

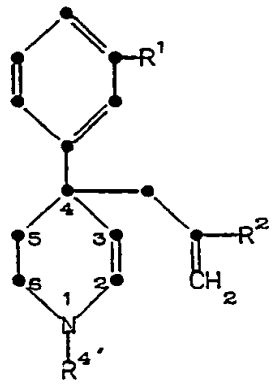
R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof.

Preferred compounds of the invention are those wherein R^1 is hydrogen, hydroxy or methoxy; R^2 and R^3 independently are hydrogen or n-C_1-C_5 alkyl; and R^4 is n-C_1-C_{10} alkyl, benzyl, 2-phenethyl, CH_2C_2-C_3 alkenyl and CH_2C_3-C_4 cycloalkyl.

This invention also provides pharmaceutical formulations useful in the treatment of pain comprising an analgesically effective amount of a 5-phenylmorphan of the above formula VI in combination with a suitable pharmaceutical carrier.

This invention also provides a 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula



II

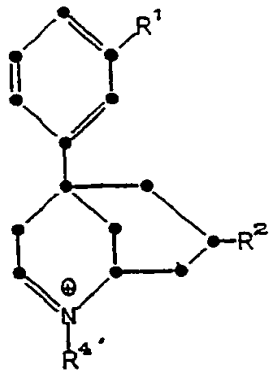
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; and

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl.

The invention also provides a 2,3-dehydro-5-phenylmorphan compound of the formula



$B^{\ominus}$ III

wherein:

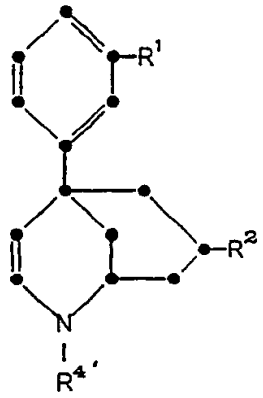
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

$B^{\ominus}$ is an anion.

The invention also provides a 3,4-dehydro-5-phenylmorphan compound of the formula



IV

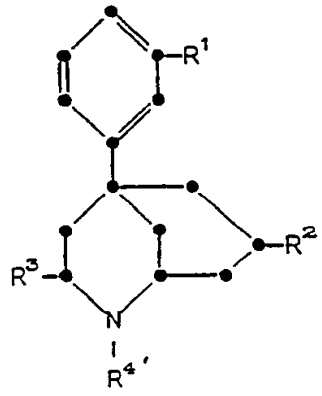
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; and

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl.

The invention also provides a process of preparing a 3-substituted-5-phenylmorphan compound having the formula



VI

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

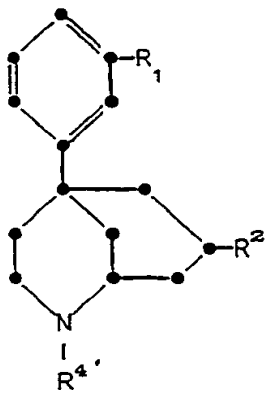
R^3 is C_1-C_5 alkyl or C_2C_2-C_4 alkenyl;

$R^{4'}$ is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by alkylating the 2,3-dehydro-5-phenylmorphanium salt of formula III wherein R^1, R^2 and $R^{4'}$ are as above with the compound R^3M where R^3 is as above and M is a cationic radical and recovering as the free base or the pharmaceutically acceptable acid addition salt thereof.

The invention also provides a process of preparing a 7-substituted-5-phenylmorphan compound having the formula



V

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by reducing the 2,3 dehydro-5-phenylmorphanium salt of formula III wherein R_1, R_2 and $R^{4'}$ are as above with a reducing agent and recovering as the free base or the pharmaceutically acid addition salt thereof.

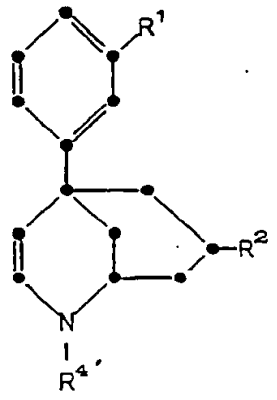
The invention also provides a process of preparing a 7-substituted-5-phenylmorphan compound having the above formula V wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmacuetically acceptable acid addition salts thereof characterized by hydrogenating a 3,4-dehydro-5-phenylmorphan compound of the formula



IV

wherein R^1, R^2 and $R^{4'}$ are as above and recovering as the free base or as the pharmaceutically acceptable acid addition salt thereof.

The invention also provides a process for preparing a 2,3,7-substituted-5-phenylmorphan compound of formula VI

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 3,7-substituted-5-phenyl-morphan of formula VI wherein R^1, R^2 and R^3 are as above and $R^{4'}$ is hydrogen with an alkylating or alkenylating agent wherein R^4 is as above other than hydrogen and recovering the free base or the pharmaceutically acceptable salt thereof.

The invention also provides a process for preparing a 5-(3-hydroxy phenyl)morphan compound of formula VI

wherein:

R^1 is hydroxy;

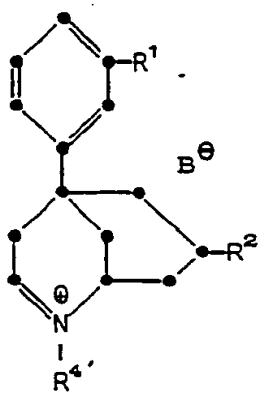
R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl, C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

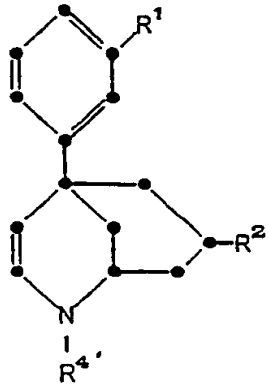
the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 5-(3-methoxy phenyl)morphan with an acid such as hydrobromic acid and acetic acid or boron tribromide followed by recovery of the free base or the pharmaceutically acceptable acid addition salt thereof.

This invention also provides a process for preparing a 2,3- or 3,4-dehydro-5-phenylmorphan compound of the formulae



III and



IV

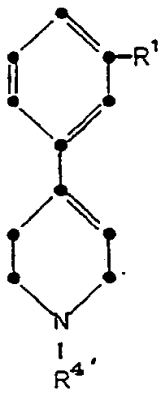
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

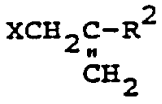
$R^{4'}$ is hydrogen or C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl; and

B is an anion characterized by reacting a 1,2,5,6-tetrahydro-4-phenylpyridine compound of the formula



I

with a propenyl alkylating agent of the formula



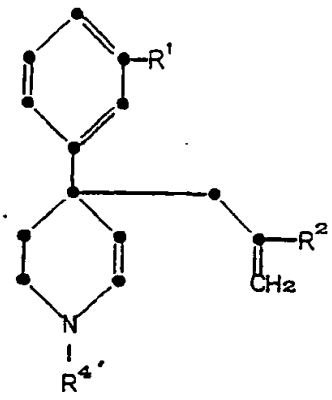
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and X is a good leaving group;

in the presence of a strong base to provide a 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula



II

wherein:

R^1, R^2 and $R^{4'}$ are the same as above and reacting said compound with a protonic acid of the formula HB', in which B' is an anion B or B" wherein the product is recovered as the salt in which B' is the anion B or as the free base of a salt in which B is exchanged for the anion B".

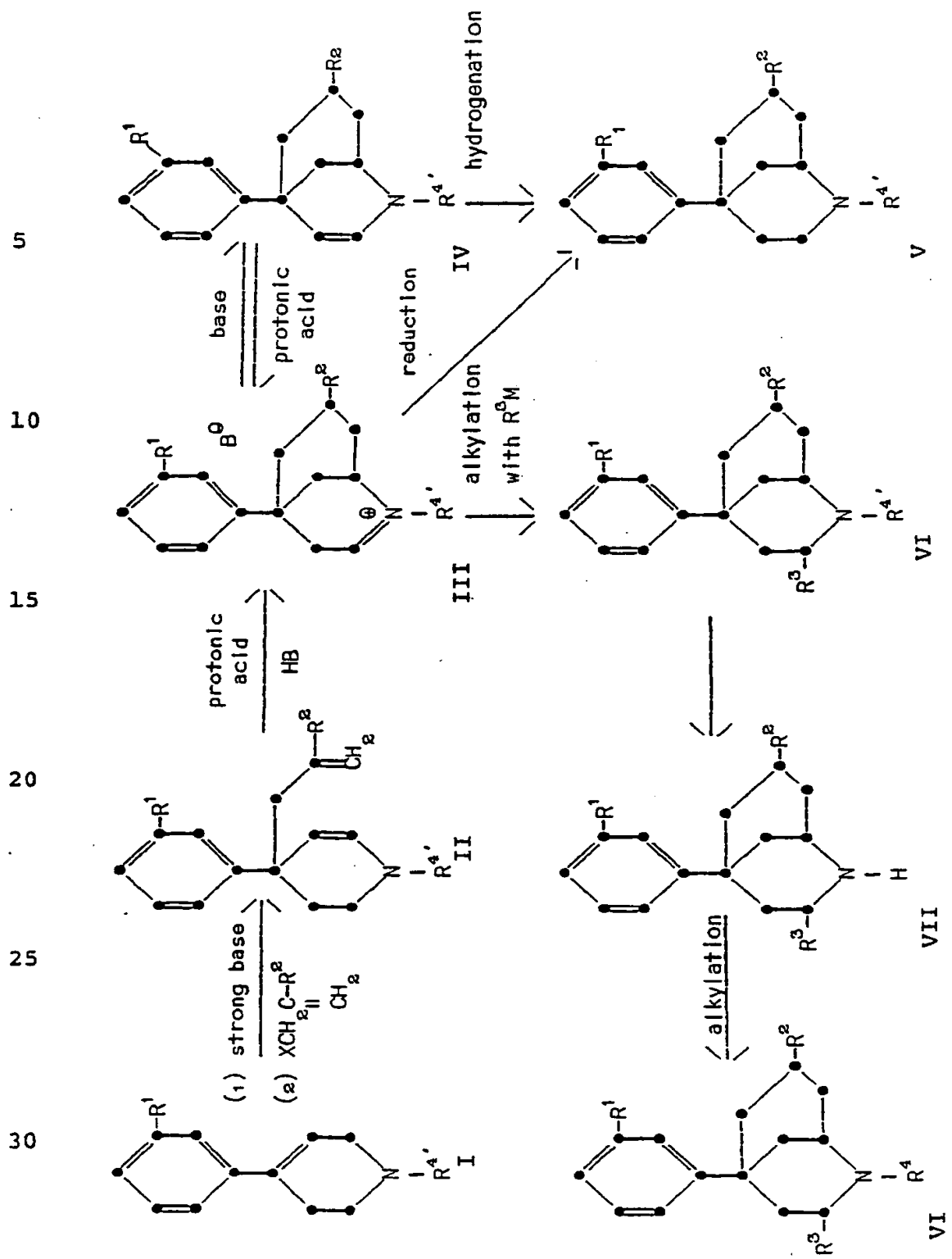
As used throughout this specification and in the appended claims, R^1 includes "C_1-C_3 alkoxy" such as methoxy, ethoxy and n-propoxy. A preferred alkoxy group is methoxy.

R^2 and R^3 are defined to include "C_1-C_5 alkyl" groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl and isopentyl, as well as "CH_2C_2-C_4 alkenyl" groups such as allyl, 3-butenyl, 2-pentenyl, 2-methyl-2-butenyl and the like.

R^4 as defined herein includes "C_1-C_{10} alkyl" groups such as methyl, ethyl, n-pentyl, isohexyl, 2-methylheptyl, 1,1-dimethylheptyl, 2-ethyloctyl, n-nonyl, n-decyl, and related alkyl groups. R^4 also includes

"C_1-C_3 phenylalkyl groups such as benzyl, 2-phenethyl and 3-phenylpropyl. The term "CH_2C_2-C_9 alkenyl" refers to groups such as allyl, 3-butenyl, 3-pentenyl, 4-hexenyl, 2,3-dimethyl-2-pentenyl, 3-octenyl, 5-decenyl and the like. R^4 additionally includes "CH_2C_3-C_6 cycloalkyl" groups such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexymethyl. Cyclopropylmethyl is a preferred cycloalkyl substituent.

The phenylmorphan compounds provided by this invention are prepared by reacting a 1-alkyl-4-phenyl-1,2,5,6-tetrahydropyridine of Formula I with a strong base such as butyl lithium or phenyl lithium and a propenyl alkylating agent such as allyl bromide to provide a 1-alkyl-4-phenyl-4-(2-propenyl)-1,4,5,6-tetrahydropyridine of Formula II. The latter compound is reacted with a protonic acid to effect ring closure with concomitant double bond migration to give a 2-alkyl-2,3-dehydro-5-phenylmorphanium salt of Formula III. Reduction of the double bond of such salt affords the corresponding 3-unsubstituted phenylmorphan of Formula V, whereas alkylation of the 2,3-dehydro-5-phenylmorphanium salt provides the corresponding 3-substituted-phenylmorphan of Formula VI the invention. The overall reaction is depicted in the following general scheme:


hydrogenation
base
protonic acid
reduction
alkylation with R^3M
protonic acid HB
(1) strong base
(2) $XCH_2C(=CH_2)-R^2$
alkylation
IV
V
III
VI
II
VII
I
VI

In the above scheme, R^1, R^2, R^3 and $R^{4'}$ are as defined hereinbefore, X is a leaving group and B and M are ionic radicals. It should be noted that when the above reactions are carried out wherein R^1 is methoxy, R^2 and R^3 both are hydrogen and $R^{4'}$ is methyl, the compound prepared is one disclosed by Rogers et al. in J. Med. Chem. 17, 1328 (1974), and is a precursor to the potent analgesic 2-methyl-5-(3-hydroxyphenyl)morphan. The process provided herein is an improvement over the prior art processes for preparing phenylmorphans since the product is produced in over fifty percent yield whereas the prior art processes produce the product in less than ten percent overall yield.

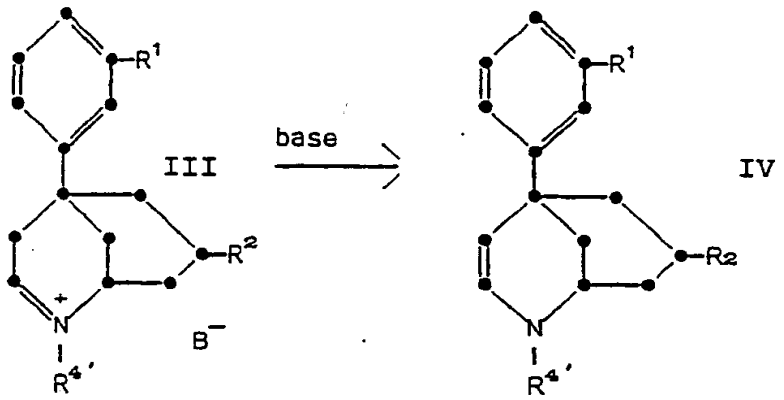
The first step in the process of this invention is the reaction of a 4-phenyl-1,2,5,6-tetrahydropyridine of Formula I with a strong base and a propenyl alkylating agent. Strong bases commonly utilized in the reaction include lower alkyl metalides such as methyl lithium, methyl sodium, n-propyl potassium, n-butyl lithium, as well as amides such as lithium diisopropylamide, sodium amide, lithium diethylamide, and hydrides such as sodium hydride. Typical propenyl alkylating agents include allyl bromide, allyl iodide, 2-methylallyl bromide, 2-ethylallyl p-toluenesulfonate, 2-n-propylallyl azide, 2-ethenylallyl iodide, 2-(2-propenyl)allyl azide, 2-(n-pentyl)allyl bromide and the like. The alkylation of the 4-phenyl-1,2,5,6-tetrahydropyridine of Formula I is carried out by first reacting the pyridine derivative with about a 1 to 20 molar excess of a strong base in an unreactive organic

solvent such as diethyl ether, tetrahydrofuran, dioxane, dichloromethane, benzene or the like. The reaction commonly is carried out at a reduced temperative of from 10 to -60°C. The tetrahydropyridine and the strong base are simply mixed together in a suitable solvent and stirred for 10 to 20 minutes, and then the reaction mixture is added to a solution containing about an equimolar amount or an excess of the appropriate propenyl alkylating agent in a suitable unreactive solvent such as diethyl ether, dioxane, or the like. The alkylation reaction typically is complete within 10 minutes to 2 hours when carried out at a temperature of from 25 to -60°C. The product is readily isolated by simply adding water or brine to the reaction mixture, separating the organic layer and then removing the organic solvent, for instance by evaporation under reduced pressure. The product, a 1-alkyl-4-allyl (or 2-alkylallyl or 2-alkenylallyl)-4-phenyl-1,4,5,6-tetrahydropyridine of Formula II, can be further purified if desired by conventional methods such as distillation, chromatography and the like.

The next step in the process of this invention comprises reacting the 1-alkyl-4-allyl (or 2-alkylallyl or 2-alkenylallyl)-4-phenyl-1,4,5,6-tetrahydropyridine of Formula II with a protonic acid to effect cyclization and concomitant double bond migration to provide a 2-alkyl-2,3-dehydro-5-phenylmorphanium salt of Formula III. Any of a number of protonic acids can be utilized to effect the cyclization and double bond migration. Commonly used acids include phosphoric acid, tetrafluoro-

boric acid, hydrochloric acid, sulfuric acid, nitric acid, para-toluenesulfonic acid, and related protonic acids. Phosphoric acid is a preferred protonic acid. The cyclization reaction generally is carried out in a solvent, typically an acidic solvent such as formic acid, acetic acid, sulfuric acid, hydrochloric acid or the like. Non-acidic solvents which can be used include dioxane, tetrahydrofuran and N,N-dimethylformamide. A preferred solvent is formic acid.

The allyl substituted tetrahydro pyridine typically is dissolved in an excess of protonic acid such as phosphoric acid in a suitable solvent such as formic acid. The reaction can be carried out at a temperature from 0°C. to 50°C., and routinely is carried out at 20°C. to 30°C. The cyclization routinely is complete within about 24 to about 72 hours. As noted in the above mechanistic scheme, the product from such protonic acid cyclization reaction is a salt, namely a 2-alkyl-2,3-dehydro-5-phenyl-7-(unsubstituted or substituted) morphanium salt of Formula III. Such intermediate salt can readily be isolated by simply removing the reaction solvent and recrystallizing the salt from common solvents such as ethyl acetate, ethanol, and the like. An alternative method for obtaining the salt intermediate in a purified form comprises first making the acidic reaction mixture basic, for instance by adding a base such as sodium hydroxide, potassium hydroxide, sodium ethoxide or butyl lithium, thereby converting the 2,3-dehydrophenylmorphanium salt of Formula III to a free base of Formula IV according to the following scheme:



wherein R^1, R^2 and $R^{4'}$ are as defined above. The 3,4-dehydrophenylmorphan free base thus formed is readily isolated by simply extracting the alkaline reaction mixture with a water immiscible solvent such as diethyl ether or chloroform, and then removing the organic solvent by evaporation. Reaction of such free base with a protonic acid converts it back again to the corresponding 2,3-dehydrophenylmorphanium salt of Formula III. Examples of typical 2-alkyl-2,3-dehydro-5-phenylmorphanium salts and 2-alkyl-3,4-dehydro-5-phenylmorphans thus prepared include the following:

2-methyl-2,3-dehydro-5-phenylmorphanium tetrafluoroborate;

2-methyl-2,3-dehydro-5-(3-methoxyphenyl)-7-methylmorphanium bromide;

2-isopropyl-2,3-dehydro-5-(3-ethoxyphenyl)-7-ethylmorphanium perchlorate;

2-cyclopropylmethyl-2,3-dehydro-5-phenyl-7-n-pentylmorphanium acetate;

2-benzyl-2,3-dehydro-5-(3-methoxyphenyl)-7-n-butylmorphanium sulfate;

2-methyl-3,4-dehydro-5-phenylmorphan;

2-ethyl-3,4-dehydro-5-(3-methoxyphenyl)-morphan;

2-isopropyl-3,4-dehydro-5-(3-ethoxyphenyl)-morphan;

2-cyclopropylmethyl-3,4-dehydro-5-(3-hydroxyphenyl)morphan;

2-benzyl-3,4-dehydro-5-phenyl-7-methyl-morphan;

2-methyl-3,4-dehydro-5-(3-methoxyphenyl)-7-ethylmorphan;

2-n-heptyl-3,4-dehydro-5-phenyl-7-n-pentylmorphan; and

2-(2-phenylethyl)-3,4-dehydro-5-(3-methoxyphenyl)-7-(3-butenyl)morphan.

The phenylmorphans of this invention which are substituted at the 3-position with an alkyl or alkenyl group are prepared by alkylation of a 2-substituted-2,3-dehydro-5-phenylmorphanium salt. Alkylating agents utilized in the reaction are defined by the formula R^3M wherein R^3 is C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl and M is a cationic radical. Commonly utilized alkylating agents include alkali metal alkyl or alkenyl metalides such as methyl lithium, ethyl sodium, n-butyl lithium, isopentyl potassium, 2-propenyl lithium, 3-butenyl sodium and related alkyl or alkenyl metalides. Additional alkylating agents which can be used are Grignard reagents of the formula

R^3 Mg halide, such as methyl magnesium bromide and n-propyl magnesium iodide, as well as dialkyl cuprates such as diethyl cuprate and diallyl cuprate.

The alkylation reaction preferably is carried out by combining the appropriate 2-substituted-2,3-dehydro-5-phenyl-(7-substituted or unsubstituted)-morphanium salt of Formula III with an equimolar amount or excess of alkylating or alkenylating agent in an unreactive organic solvent such as diethyl ether, diisopropyl ether, dioxane, tetrahydrofuran or the like. The reaction generally is complete within two to ten hours when carried out at 20 to 40°C. The product, a 2,3-disubstituted-5-phenyl-(7-substituted or unsubstituted)morphan of Formula VI, is isolated by diluting the reaction mixture with aqueous ammonium chloride and then washing the organic layer several times with water. Separation of the organic layer and evaporation of the solvent therefrom then provides the product as a solid or an oil. Further purification can be accomplished if desired by routine methods such as column chromatography, crystallization, salt formation and the like.

The phenylmorphans of this invention which are unsubstituted at the 3-position can be prepared by reduction of a 2,3-dehydro-5-phenylmorphanium salt of Formula III. For example, a salt such as 2-benzyl-2,3-dehydro-5-(3-ethoxyphenyl)-7-ethylmorphanium tetrafluoroborate can be reacted with about an equimolar quantity or excess of a reducing agent such as sodium borohydride or lithium aluminum hydride to provide the corresponding saturated phenylmorphan, i.e.

2-benzyl-5-(3-ethoxyphenyl)-7-ethylmorphan.

Such 3-unsubstituted phenylmorphans can alternatively be prepared by catalytic hydrogenation of the aforementioned 3,4-dehydro-5-phenylmorphans. For example, a compound such as 2-cyclopropylmethyl-3,4-dehydro-5-(3-hydroxyphenyl)-7-isobutylmorphan can be hydrogenated in the presence of a suitable catalyst to provide 2-cyclopropylmethyl-5-(3-hydroxyphenyl)-7-isobutylmorphan. The catalytic hydrogenation reactions typically are carried out in organic solvents such as methanol or ethanol, and with common catalysts such as palladium on carbon, platinum, Raney nickel and the like. When the reaction is carried out at 20 to 50°C. with a hydrogen pressure of 30 to 80 psi, the reduction is substantially complete after one-half to twenty-four hours. The reduced product is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The phenylmorphan thus formed can be further purified if desired by routine methods such as crystallization, chromatography and salt formation.

Certain of the phenylmorphans provided by this invention are useful both as analgesics and as intermediates leading to other phenylmorphans. For example, the 2-methyl-phenylmorphans of the invention can be demethylated to provide the corresponding 2-unsubstituted phenylmorphan, which then can be alkylated with any R^4 alkylating agent to give the other compounds of the invention. Such demethylation is accomplished by reacting the 2-methyl-phenylmorphan with a halofor-

mate to provide a carbamate, which is then converted to the demethylated product upon reaction with a base such as sodium or potassium hydroxide. The demethylation reaction thus contemplated is described in detail in U.S. Patent No. 4,081,450.

The 2-benzyl-5-phenylmorphans of the invention also can be converted to 2-unsubstituted phenylmorphans which can subsequently be alkylated as desired. Debenzylation is accomplished by catalytic hydrogenation in the presence of a suitable catalyst such as platinum or palladium. For example, a phenylmorphan such as 2-benzyl-3-ethyl-5-(3-methoxyphenyl)-7-methylmorphan can be hydrogenated in the presence of palladium on carbon in ethanol for two hours at 50°C. under a hydrogen atmosphere of 60 psi to effect debenzylation and thus afford 3-ethyl-5-(3-methoxyphenyl)-7-methylmorphan.

The 2-unsubstituted phenylmorphans of the invention are particularly useful as intermediates in the synthesis of other compounds of the invention. Normal alkylation with a C_1-C_{10} alkyl, CH_2C_2-C_9 alkenyl, C_1-C_3 alkylphenyl or CH_2C_3-C_6 cycloalkyl alkylating agent affords the analgesically active phenylmorphans of this invention. For example, an alkylating agent such as allyl bromide can be reacted with a phenylmorphan such as 3-ethyl-5-phenyl-7-methylmorphan to provide 2-allyl-3-ethyl-5-phenyl-7-methylmorphan. Such alkylation reactions generally are carried out in a solvent such as dioxane or tetrahydrofuran and usually in the presence of a base such

as triethylamine or pyridine to act as an acid scavenger. The reactions normally are complete after two to four hours when carried out at 30 to 100°C. The alkylated product is readily recovered by adding the reaction mixture to water and then extracting the aqueous mixture with a solvent such as diethyl ether, and then evaporating the organic solvent. The product thus formed can be purified by crystallization, chromatography, salt formation and the like.

The phenylmorphan compounds of this invention which have a hydroxyl substituent in the phenyl 3-position (i.e. R^1 is hydroxy) are preferably prepared from the corresponding 3-methoxyphenylmorphan by cleavage of the methyl ether moiety. Such cleavage generally is accomplished by reaction of a 3-methoxyphenylmorphan with acids such as hydrobromic acid and acetic acid or boron tribromide. For instance, a phenylmorphan such as 2-benzyl-3,7-diethyl-5-(3-methoxyphenyl)morphan can be dissolved in a mixture of hydrobromic acid and acetic acid and heated at reflux for two to twenty hours. The reaction mixture next is made alkaline and the product is extracted into a solvent such as diethyl ether to provide, after removal of the solvent, the corresponding 3-hydroxyphenylmorphan derivative, namely 2-benzyl-3,7-diethyl-5-(3-hydroxyphenyl)morphan.

The phenylmorphans contemplated herein are basic in nature by virtue of the indocyclic amino group located in the 2-position. Because of such basic nature, the compounds readily form acid addition salts with any of a number of organic and inorganic acids.

The pharmaceutically acceptable acid addition salts so formed are provided as an additional aspect of this invention. Such salts are those which are substantially non-toxic and can be administered to animals, including humans, for the relief of pain. The salts provided by this invention are prepared by reacting a phenylmorphan with any of a number of organic acids such as acetic acid, succinic acid, maleic acid, citric acid, p-toluenesulfonic acid, benzoic acid, as well as with any of a number of inorganic acids, including hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and related acids. The pharmaceutically acceptable acid addition salts are generally highly crystalline and lend themselves to convenient purification by recrystallization from common solvents such as ethanol, water, acetone and the like.

The following listing of compounds is illustrative of the phenylmorphans provided by this invention:

2,3-dimethyl-5-(3-hydroxyphenyl)-7-ethylmorphan;

2-(2-phenylethyl)-3,7-dimethyl-5-(3-methoxyphenyl)morphan;

2-allyl-3-ethyl-5-phenylmorphan;

2-cyclobutylmethyl-3-allyl-5-(3-methoxyphenyl)-7-ethylmorphan;

2-cyclohexylmethyl-5-phenyl-7-methylmorphan;

2-(3-hexenyl)-3,7-diisopropyl-5-(3-n-propoxyphenyl)morphan;

2-(3-phenylpropyl)-3-methyl-5-(3-ethoxyphenyl)morphan;

2-n-octyl-3,7-dimethyl-5-phenylmorphan;

2-(3-ethylhexyl)-3-(2-butenyl)-5-(3-hydroxyphenyl)-7-ethylmorphan;

2-benzyl-3,7-di-n-propyl-5-(3-hydroxyphenyl)-morphan;

2-(2,3-dimethylheptyl)-3-ethyl-5-phenyl-7-methylmorphan;

2-(2-phenylethyl)-3,7-dimethyl-5-(3-hydroxyphenyl)morphan;

2-methyl-3,7-diethyl-5-phenylmorphanium bromide;

2,3,7-triethyl-5-(3-methoxyphenyl)morphanium chloride;

2-n-butyl-3-methyl-5-(3-hydroxyphenyl)morphanium acetate;

2-isopentyl-3-ethyl-5-(3-ethoxyphenyl)morphanium phosphate;

2-cyclopropylmethyl-3-methyl-5-phenyl-7-ethylmorphanium sulfate;

2-methyl-3-n-propyl-5-phenyl-7-(3-butenyl)-morphanium formate;

2,7-dimethyl-3-(2-pentenyl)-5-(3-methoxyphenyl)morphanium benzoate;

2-benzyl-3,7-diethyl-5-phenylmorphanium succinate;

2-isopropyl-3,7-dimethyl-5-(3-hydroxyphenyl)-morphanium p-toluenesulfonate;

2-allyl-3-(3-pentenyl)-5-(3-n-propoxyphenyl)-7-(2-butenyl)morphanium fumarate; and related compounds.

The phenylmorphan derivatives provided by this invention are useful as analgesics in the treatment of pain in animals suffering from pain and in need of treatment. The compounds have demonstrated their pain-relieving capacity in standard biological evaluations designed to measure analgesic activity. One such test is the rat-tail jerk assay. In this test, a light beam or heat source is applied to the tail of a rat. The pain threshold of the animal is measured by the latency of the rat to remove its' tail from the pain source. Column 2 in the following table presents the effective subcutaneous dose in mg/kg of a number of the compounds of this invention which causes a two second delay (ED_2 sec) in tail removal compared to the control animals receiving no drug.

In another test designed to show analgesic activity, mice are given an intraperitaneal injection of acetic acid which causes the animals to writh. An effective analgesic is one that reduces the writhings. Column 3 of the following table presents the effective subcutaneous and oral doses in mg/kg of a compound of this invention required to reduce the writing in test animals by fifty percent (ED_{50}).

Table I

Column I	Column II	Column III	
Compound administered	Rat tail jerk subcutaneous injection mg./kg ED_2 seconds	Mouse writhing s.c. mg/kg ED_{50}	Mouse writhing oral mg/kg ED_{50}
2-methyl-5-(3-methoxyphenyl)-morphan	10.0	9.6	27.5
2-methyl-5-(3-hydroxyphenyl)-morphan	1.0	1.3	29.0
2,7-dimethyl-5-(3-methoxyphenyl)-morphan	10.0	3.5	28.5
2,7-dimethyl-5-(3-hydroxyphenyl)-morphan	0.5	0.72	28.5
2,3-dimethyl-5-(3-methoxyphenyl)-morphan	15.0	13.0	17.0
2,3-dimethyl-5-(3-hydroxyphenyl)-morphan	2.0	2.0	23.0
2,3,7-trimethyl-5-(3-methoxyphenyl)morphan	20.0	7.8	22.0
2,3,7-trimethyl-5-(3-hydroxyphenyl)morphan	0.5	0.66	14.0

The phenylmorphans of this invention can be administered to humans suffering from pain and in need of relief. The compounds are effective as analgesics when administered orally or parenterally. The invention accordingly provides an analgesic method which comprises administering to a subject suffering from pain and in need of treatment an analgesically effective dose of a phenylmorphan defined by the above general formula. The compounds preferably are administered orally in the form of pharmaceutically acceptable acid addition salts. The dosage required to effect analgesia will vary somewhat depending upon the route of administration, the severity of the pain to be alleviated, as well as the particular analgesic agent selected to be administered. A typical oral dose will range from 0.5 to 25 mg/kg. The compounds can also be administered parenterally via the intramuscular, intravenous or subcutaneous routes. Typical parenteral doses will range from 0.1 mg/kg to 20 mg/kg. In severe cases of pain, the phenylmorphan may be administered via the intramuscular or intravenous routes, while maintenance therapy may be conveniently accomplished by oral dosing.

A further embodiment of this invention are pharmaceutical formulations comprising an analgesicially effective amount of a phenylmorphan having the above general formula in combination with any of a number of suitable diluents, excipients, carriers and the like. The formulations generally will contain from 5 to 50 percent by weight of active ingredient. Commonly used diluents and carriers include lactose, sucrose, starch

powder, talc, magnesium stearate, magnesium oxide, calcium sulfate, acacia powder, gelatin, sodium algivate, sodium benzoate, stearic acid, and related adjuvants routinely used in formulation of pharmaceuticals. The phenylmorphans of this invention can be formulated as tablets, capsules, buccal seals, lozenges, and the like for oral administration. The compounds are conveniently formulated in aqueous saline or dextrose to constitute an injectable liquid solution for parenteral administration via the intravenous or intramuscular routes. Alternatively, the phenylmorphans can be dissolved in a suitable solvent such as water or ethanol and placed in a vial and lyophilized to provide a dry powder that is ready for reconsitution by the addition of a suitable amount of water, saline or the like. If desired, the formulations of this invention can contain additional analgesic agents such as propoxyphene hydrochloride or the like.

The following detailed examples are provided to illustrate various specific aspects of the invention.

Example 1

1-Methyl-4-allyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine

A solution of 74 ml. of 1.6 M n-butyl lithium was added dropwise to a cold (0°C.) stirred solution of 24.36 g. of 1-methyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine in 300 ml. of tetrahydrofuran. The reaction mixture was stirred for 10 minutes at 0°C. and then added dropwise over thirty minutes to a stirred cold

(-50°C.) solution of allyl bromide in 250 ml. of diethyl ether. The reaction mixture was warmed to 0°C. and then diluted with 500 ml. of aqueous sodium chloride solution. The organic layer was separated, diluted with an additional 2 liters of diethyl ether, washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided 33 g. of the crude product as an oil. The oil was distilled twice to provide 17.91 g. of 1-methyl-4-allyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine. B.P. 120-123°C. at 0.1 torr.

Analysis calc. for $C_{16}H_{21}NO$

Theory: C, 78.97; H, 8.70; N, 5.76.

Found: C, 78.72; H, 8.55; N, 5.48.

Example 2

2-Methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan

A solution of 1.0 g. of 1-methyl-4-allyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine dissolved in 2.5 ml. of 85.8 percent aqueous phosphoric acid and 2.5 ml. of formic acid was stirred for sixty-six hours at 24°C. under a nitrogen atmosphere. The reaction mixture then was diluted with 150 ml. of ice water and made alkaline by the addition of 50 percent aqueous sodium hydroxide. The product was extracted from the alkaline solution into diethyl ether. The ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 950 mg. of 2-methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan.

Mass spec. Theory 243, Found 243.

Example 3

2-Methyl-5-(3-methoxyphenyl)morphan

A solution of 4.0 g. of 2-methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan in 150 ml. of ethanol containing 1.5 g. of five percent palladium on carbon was stirred for eighteen hours at 24°C. under a hydrogen pressure of 60 psi. The reaction mixture then was filtered and the solvent was evaporated from the filtrate to provide 3.72 g. of 2-methyl-5-(3-methoxyphenyl)morphan.

The product thus obtained was dissolved in 60 ml. of isopropanol and the solution was saturated with hydrogen bromide to form 3.22 g. of a white precipitate. The precipitated salt was recrystallized from 20 ml. of diisopropyl ether and 40 ml. of isopropanol to provide 1.0 g. of 2-methyl-5-(3-methoxyphenyl)-morphanium bromide. M.P. 152.5-154°C.

Analysis calc. for $C_{16}H_{24}BrNO$

Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 59.19; H, 7.13; N, 4.04.

Example 4

2-Methyl-5-(3-hydroxyphenyl)morphan

A solution of 2.22 g. of 2-methyl-5-(3-methoxyphenyl)morphanium bromide dissolved in a mixture of 30 ml. glacial acetic acid and 30 ml. of 48 percent aqueous hydrobromic acid was heated at reflux for sixteen hours. The reaction mixture then was cooled to room temperature, diluted with 100 ml. of water and made alkaline to pH 9.5 with sodium hydroxide solution. The

alkaline solution was extracted with diethyl ether, and the ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided 1.29 g. of the product as a syrup. The syrup was dissolved in 25 ml. of diisopropyl ether and 125 ml. of isopropanol, and the solution was saturated with hydrogen bromide. The precipitate which formed was collected by filtration and dried to afford 1.0 g. of 2-methyl-5-(3-hydroxyphenyl)morphanium bromide. M.P. 207-208.5°C.

Analysis calc. for $C_{15}H_{22}BrNO$

Theory: C, 57.70; H, 7.10; N, 4.49.

Found: C, 57.45; H, 6.87; N, 4.25.

Example 5

1-Methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6-tetrahydropyridine

A solution of 74 ml. of 1.6 molar n-butyl lithium in tetrahydrofuran was added dropwise to a cold stirred solution of 24.36 g. of 1-methyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine in 300 ml. of tetrahydrofuran. After the addition was complete and the reaction mixture had been stirred at 0°C. for ten minutes, the mixture was added dropwise over thirty minutes to a stirred cold (-50°C.) solution of 10.86 g. of 3-chloro-2-methylpropene (methallyl chloride) in 250 ml. of diethyl ether. The reaction mixture was stirred and allowed to warm slowly to 0°C., at which time the reaction mixture was diluted by the dropwise addition of 500 ml. of saturated aqueous sodium chloride solution. The organic layer next was separated, diluted

with 2 liters of fresh diethyl ether, washed with fresh water and dried. Removal of the solvent by evaporation under reduced pressure then provided 33.43 g. of an oil, which after distillation gave 20.97 g. of 1-methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6-tetrahydropyridine. B.P. 138-141°C. at 0.1 torr. Mass spec. Theory: 257; Found M^+ 257.

Example 6

2,7-Dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate

Twenty grams of 1-methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6,-tetrahydropyridine were dissolved in 50 ml. of 85.8% aqueous phosphoric acid containing 50 ml. of formic acid. The reaction mixture was stirred for forty-eight hours at ambient temperature, and then diluted by the addition of 300 ml. of ice water. Fifty percent aqueous sodium hydroxide was added to the aqueous reaction mixture to pH 11, and then the product was extracted therefrom into diethyl ether. The ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 21 g. of crude oil, which after distillation gave 17.68 g. of 2,7-dimethyl-3,4-dehydro-5-(3-methoxyphenyl)morphan. B.P. 130-138°C. at 0.1 torr.

Excess perchloric acid was added to a solution of 12.68 g. of the compound thus prepared dissolved in diethyl ether. The precipitated salt which formed was collected and recrystallized from 200 ml. of ethanol to afford 12.82 g. of 2,7-dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate. M.P. 131-133°C.

Example 7

2,7-Dimethyl-5-(3-methoxyphenyl)morphan

A solution containing 5 g. of 2,7-dimethyl-3,4-dehydro-5-(3-methoxyphenyl)morphan dissolved in 200 ml. of ethanol containing 5 g. of five percent palladium on carbon was stirred for twenty-four hours at about 24°C. under hydrogen at 60 psi. The reaction mixture then was filtered and the solvent was removed from the filtrate by evaporation to give 4.8 g. of an oil. The oil was then dissolved in 100 ml. of diethyl ether and the solution was saturated with hydrogen bromide to effect salt formation. The salt precipitated out of solution and was collected and recrystallized from 30 ml. of diisopropyl ether and 25 ml. of isopropanol to provide 1.78 g. of 2,7-dimethyl-5-(3-methoxyphenyl)morphanium bromide. M.P. 178-181°C.

Analysis calc. for $C_{17}H_{26}BrNO$

Theory: C, 60.00; H, 7.70; N, 4.12.

Found: C, 59.74; H, 7.47; N, 4.38.

Example 8

2,7-Dimethyl-5-(3-hydroxyphenyl)morphan

Following the procedure set forth in Example 4, 1.1 g. of 2,7-dimethyl-5-(3-methoxyphenyl)morphan was dissolved in a solution of 15 ml. of 48 percent hydrobromic acid and 15 ml. of glacial acetic acid, and the reaction mixture was heated at reflux for sixteen hours. Normal workup of the reaction mixture afforded 710 mg. of the product as an oil, which then was converted to its hydrobromide salt. Recrystallization of

the salt from 30 ml. of diisopropyl ether and 20 ml. of isopropanol afforded 620 mg. of 2,7-dihydroxy-5-(3-hydroxyphenyl)morphanium bromide. M.P. 239-241.5°C.

Analysis calc. for $C_{16}H_{24}BrNO$

Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 59.11; H, 7.30; N, 4.50.

Example 9

2,3,7-Trimethyl-5-(3-methoxyphenyl)morphan

To a stirred solution of 60 ml. of 1.6 molar methyl lithium in diethyl ether at 24°C. was added portionwise over thirty minutes 6.0 g. of 2,7-dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate (from Example 6). The reaction mixture was stirred at 24°C. for two hours following complete addition of the salt. The reaction mixture next was diluted by the addition of 30 ml. of saturated aqueous ammonium chloride, and the organic layer then was separated, washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 4.79 g. of the product as an oil. The oil was converted to the hydrobromide salt by reaction with hydrogen bromide in diethyl ether. The salt thus formed was recrystallized from 100 ml. of diisopropyl ether and 250 ml. of isopropanol to give 3.18 g. of 2,3,7-trimethyl-5-(3-methoxyphenyl)morphanium bromide. M.P. 191-194°C.

Analysis calc. for $C_{18}H_{28}BrNO$

Theory: C, 61.02; H, 7.97; N, 3.95.

Found: C, 61.01; H, 7.79; N, 4.20.

Example 10

2,3,7-Trimethyl-5-(3-hydroxyphenyl)morphan

Two grams of 2,3,7-trimethyl-5-(3-methoxyphenyl)morphan was reacted with hydrobromic acid and acetic acid according to the procedure set out in Example 4 to provide 1.43 g. of the title compound as a solid substance. The compound was purified by crystallization from 50 ml. of ethyl acetate and 15 ml. of ethanol to give 1.17 g. of 2,3,7-trimethyl-5-(3-hydroxyphenyl)morphan. M.P. 193°C. (dec.).

Analysis calc. for $C_{17}H_{25}NO$

Theory: C, 78.72; H, 9.71; N, 5.40.

Found: C, 78.61; H, 9.54; N, 5.20.

Example 11

2,3-Dimethyl-5-(3-methoxyphenyl)morphan

Eight grams of 2-methyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate were reacted with 75 ml. of 1.6 molar methyl lithium in diethyl ether according to the general procedure set out in Example 9 to give 6.33 g. of 2,3-dimethyl-5-(3-methoxyphenyl)-morphan. B.P. 140-143°C. at 0.1 torr.

The compound thus formed was converted to its hydrobromide salt by reaction with excess hydrogen bromide in diethyl ether. The salt which precipitated was collected and recrystallized twice from 25 ml. of diisopropyl ether and 100 ml. of isopropanol to give 2.79 g. of 2,3-dimethyl-5-(3-methoxyphenyl)morphanium bromide. M.P. 192.5-194°C.

Analysis calc. for $C_{17}H_{24}BrNO$

Theory: C, 60.00; H, 7.77; N, 4.12.

Found: C, 59.87; H, 7.50; N, 4.11.

Example 12

2,3-Dimethyl-5-(3-hydroxyphenyl)morphan

Two grams of 2,3-dimethyl-5-(3-methoxyphenyl)-morphanium bromide were reacted with 25 ml. of 48 percent hydrobromic acid and 25 ml. of acetic acid according to the procedure of Example 4 to give, after purification by salt formation and recrystallization, 900 mg. of 2,3-dimethyl-5-(3-hydroxyphenyl)morphanium bromide. M.P. 237-239°C.

Analysis calc. for $C_{16}H_{24}BrNO$

Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 58.69; H, 7.21; N, 4.49.

Example 13

3,7-Dimethyl-5-(3-methoxyphenyl)morphan

To a solution of 2,3,7-trimethyl-5-(3-methoxyphenyl)morphan in dichloromethane is added a solution of phenyl chloroformate in dichloromethane. The reaction mixture is stirred for several hours at ambient temperature, and then the solvent is removed by evaporation. The residue is made alkaline by the addition of sodium hydroxide, and the alkaline solution is heated for several hours. After cooling to room temperature, the alkaline reaction mixture is extracted several times with diethyl ether. The ethereal extracts are combined, washed with water and dried. Evaporation of the solvent affords 3,7-dimethyl-5-(3-methoxyphenyl)morphan.

Example 14

2-Cyclopropylmethyl-3,7-dimethyl-5-(3-methoxyphenyl)-morphan

A solution of cyclopropylmethyl bromide in tetrahydrofuran containing 3,7-dimethyl-5-(3-methoxyphenyl)morphan and triethylamine is heated for several hours. The reaction mixture is then washed with water, and the organic solvent is next removed by evaporation under reduced pressure to provide 2-cyclopropylmethyl-3,7-dimethyl-5-(3-methoxyphenyl)morphan.

Example 15

2-Benzyl-5-phenyl-7-ethylmorphan

A solution of 1-benzyl-4-phenyl-1,2,5,6-tetrahydropyridine in tetrahydrofuran containing n-butyl lithium is added to a solution of 3-chloro-2-ethylpropene in tetrahydrofuran. The reaction is carried out according to the procedure of Example 1 to give 1-benzyl-4-phenyl-4-(2-ethylallyl)-1,4,5,6-tetrahydropyridine. The latter compound is reacted with phosphoric acid and formic acid to give, after treatment with sodium hydroxide, 2-benzyl-3,4-dehydro-5-phenyl-7-ethylmorphan. Catalytic hydrogenation of the latter compound provides 2-benzyl-5-phenyl-7-ethylmorphan.

Example 16

2-Allyl-3-isopropyl-5-phenyl-7-ethylmorphan

A solution of 2-benzyl-3,4-dehydro-5-phenyl-7-ethylmorphan in diethyl ether is added to a stirred ethereal solution of isopropyl lithium according to

the method of Example 9 to give 2-benzyl-3-isopropyl-5-phenyl-7-ethylmorphan. Catalytic hydrogenation of the latter compound effects debenzylation to provide 3-isopropyl-5-phenyl-7-ethylmorphan. Allyl bromide is reacted with the latter compound to effect N-alkylation to provide 2-allyl-3-isopropyl-5-phenyl-7-ethylmorphan.

Example 17

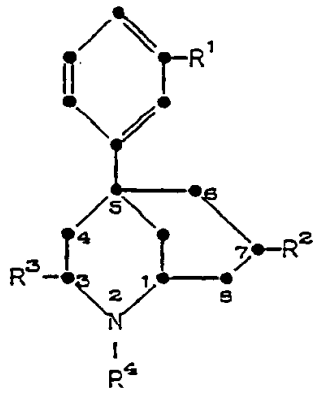
The following ingredients are combined and molded into tablets for convenient oral administration to a subject suffering from pain and in need of treatment.

2-cyclopropylmethyl-3,7-dimethyl-5-(3-hydroxyphenyl)morphanium chloride	1000 mg.
dextrose	3500 mg.
starch powder	500 mg.
	5000 mg.

The above formulation is compressed into 25 tablets each containing 40 mg. of active ingredient. Such tablets are administered to a person needing analgesic treatment at the rate of from 1 to about 4 tablets per day.

CLAIMS

1. A 5-phenylmorphan compound having the formula



VI

wherein:

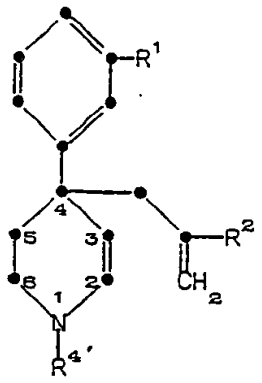
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof.

2. A 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula



II

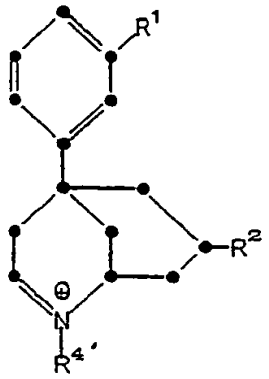
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; and

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl.

3. A 2,3-dehydro-5-phenylmorphan compound of the formula



III

wherein:

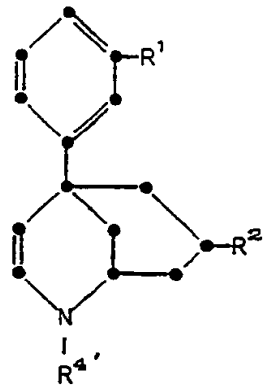
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

$B^{\ominus}$ is an anion.

4. A 3,4-dehydro-5-phenylmorphan compound of the formula



IV

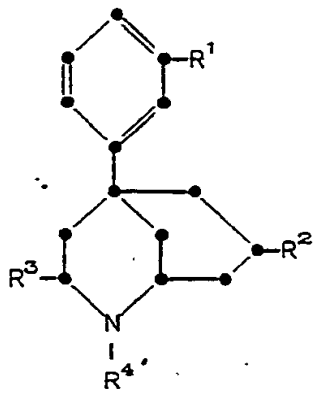
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; and

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl.

5. A process of preparing a 3-substituted-5-phenylmorphan compound having the formula



VI

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

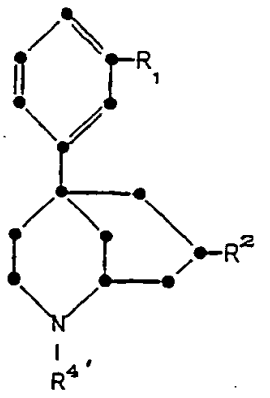
R^3 is C_1-C_5 alkyl or C_2C_2-C_4 alkenyl;

$R^{4'}$ is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by alkylating the 2,3-dehydro-5-phenylmorphanium salt of formula III of claim 12 wherein R^1, R^2 and $R^{4'}$ are as above with the compound R^3M where R^3 is as above and M is a cationic radical and recovering as the free base or the pharmaceutically acceptable acid addition salt thereof.

6. A process of preparing a 7-substituted-5-phenylmorphan compound having the formula



V

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by reducing the 2,3 dehydro-5-phenylmorphanium salt of formula III of claim 12 wherein R_1, R_2 and $R^{4'}$ are as above with a reducing agent and recovering as the free base or the pharmaceutically acid addition salt thereof.

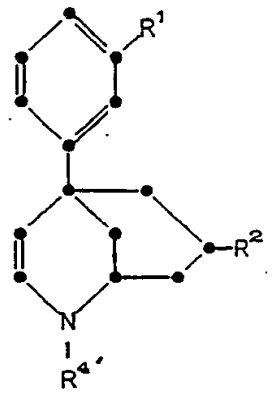
7. A process of preparing a 7-substituted-5-phenylmorphan compound having the formula V of claim 6 wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof characterized by hydrogenating a 3,4-dehydro-5-phenylmorphan compound of the formula



IV

wherein R^1, R^2 and $R^{4'}$ are as above and recovering as the free base or as the pharmaceutically acceptable acid addition salt thereof.

8. A process for preparing a 2,3,7-substituted-5-phenylmorphan compound of formula VI of claim 1

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 3,7-substituted-

5-phenyl-morphan of formula VI wherein R^1, R^2 and R^3 are as above and R^4 is hydrogen with an alkylating or alkenylating agent wherein R^4 is as above other than hydrogen and recovering the free base or the pharmaceutically acceptable acid salt thereof.

9. A process for preparing a 5-(3-hydroxy phenyl)morphan compound of formula VI of claim 1 wherein:

R^1 is hydroxy;

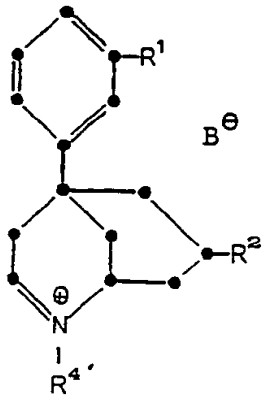
R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl, C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

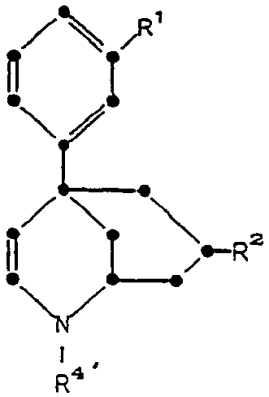
the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 5-(3-methoxy phenyl)morphan with an acid such as hydrobromic acid and acetic acid or boron tribromide followed by recovery of the free base or pharmaceutically acceptable acid addition salt thereof.

10. A process for preparing a 2,3- or 3,4-dehydro-5-phenylmorphan compound of the formulae



III and



IV

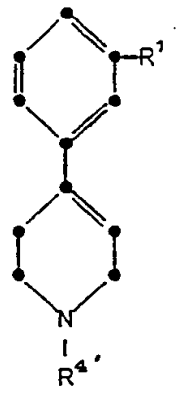
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

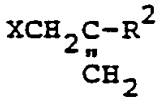
$R^{4'}$ is hydrogen or C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or CH_2C_3-C_6 cycloalkyl; and

B is an anion characterized by reacting a 1,2,5,6-tetrahydro-4-phenylpyridine compound of the formula



I

with a propenyl alkylating agent of the formula



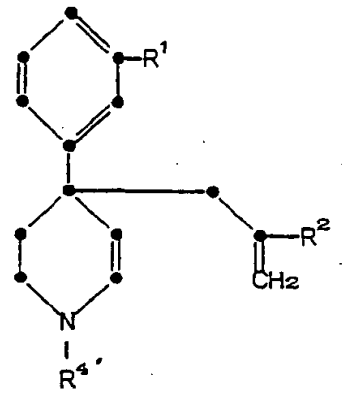
wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or CH_2C_2-C_4 alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or CH_2C_3-C_6 cycloalkyl; and X is a good leaving group;

in the presence of a strong base to provide a 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula



II

wherein:

R^1, R^2 and $R^{4'}$ are the same as above and reacting said compound with a protonic acid of the formula HB', in which B' is an anion B or B" wherein the product is recovered as the salt in which B' is the anion B or as the free base of a salt in which B is exchanged for the anion B".

11. A pharmaceutical formulation useful in the treatment of pain comprising an analgesically effective amount of a 5-phenylmorphan compound of formula VI according to claim 1 in combination with a suitable pharmaceutical carrier thereof.

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European Patent Office
Office européen des brevets

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A3

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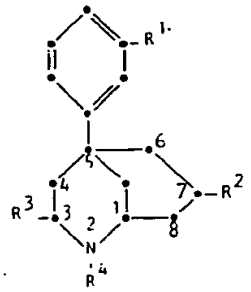
(54) **Phenylmorphans, processes for their preparation, pharmaceutical compositions containing them, and 4-phenyl-tetrahydro-pyridines.**

(57) A novel 5-phenylmorphan compound having the formula



V1

wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 and R^3 independently are hydrogen, C_1-C_8 alkyl or CH_2C_2-C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, CH_2C_2-C_9 alkenyl, or CH_2C_3-C_6 cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof are disclosed. These compounds are useful in the treatment of pain.

EP 0 018 077 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 80 30 0746

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
	JOURNAL OF MEDICINAL CHEMISTRY, vol. 20, no. 2, February 1977, pages 221-228 Washington US M. TAKEDA et al.: "Azabicycloalkanes as Analgetics. 3.1 Structure Activity Relationships of 1-Phenyl-6-azabicyclo (3.2.1) octanes and Absolute Stereochemistry of (+)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo(3.2.1.)octane and its 7-endo-methyl derivative" * Whole paper, particularly page 221, right-hand column, paragraph 3 *	1,3, 4,11	C 07 D 221/22 A 61 K 31/435// C 07 D 211/70
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	US - A - 4 081 450 (D.M. ZIMMERMAN) * Whole patent *	2	C 07 D 221/22 221/70
	--		
D	JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 1, January 1974, pages 133-134 Washington US H.H. ONG: "Phenylmorphan agonists-anagonists" * Whole paper *	1,11	TECHNICAL FIELDS SEARCHED (Int.Cl.³)

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant
- A: technological background
- O: non-written disclosure
- P: intermediate document
- T: theory or principle underlying the invention
- E: conflicting application
- D: document cited in the application
- L: citation for other reasons
- &: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	09-09-1980	ALLARD

EPO Form 1503.1 06.78

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,

namely:

1) Claims 1,5-9,11: 5-phenylmorphans, processes for their preparation and their use in pharmaceuticals.
2) Claim 2: 4-phenyltetrahydropyridines (starting compound)
3) Claims 3,4,10: 5-phenyl-dehydromorphans and process for their preparation (intermediates).

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims: